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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/697,329	10/27/2000	Eiichi Iishi	1422-449P	8402

7590 09/17/2004

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EXAMINER	
HABTE, KAHSAY	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/697,329	IISHI ET AL.	
	Examiner	Art Unit	
	Kahsay Habte, Ph. D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 12-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *16 and 17* is/are allowed.

6)☒ Claim(s) *7 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAIL ACTION

1. Claims 7 and 12-17 are pending.

2. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaspersen *et al.* {Journal of Label. comp. and Radiopharm., 27, No. 9, 1055 (1989)} in view of Khankari et al. {Thermochemica Acta 248 (1995) 61-79}. Kaspersen et *al.* teaches the multi-step synthesis of Org-3770 (mirtazapine) on page 1058 (Fig.4). On page 1066, Kaspersen *et al.* teaches the synthesis of mirtazapine and the crystallization of the mirtazapine (compound **1c**) from the crude product using methanol/water solvent mixture to achieve colorless crystals. The only difference between applicant's mirtazapine hydrate and Kaspersen's Org-3770 hydrate is that Kaspersen's hydrate is ^{13}carbon labeled, but the instantly claimed product requires that the mirtazapine be unlabeled. The structure of Kaspersen's mirtazapine and the

structure of applicants unlabeled mirtazapine are extremely closely related. Just as the labeled compound clearly suggests the unlabelled so do the labeled hydrate clearly suggest the unlabelled hydrate. This is particularly true since the labeled compound was prepared in order to study what the known unlabelled compound does in the body. As shown in Khanakari et al., hydration alters pharmaceutically important properties such as solubility and the physical and chemical stability of pharmaceutical solids that contributes in the modification of bioavilability and product performance (see page 64). It is obvious to one skilled in the art to modify the labeled Kaspersen's mirtazapine hydrate to a hydrated unlabeled mirtazapine compound, since hydration alters the physical chemical or biological performance of a pharmaceutical drug (e.g. bioavailability, solubility, stability) and the fact that hydrates are a conventional form of making a pharmaceutical composition as shown in Khankari et al. (see page 77, last paragraph). Thus, the prior art teaching that mirtazapine forms a hydrate in the labeled form would suggest that mirtazapine forms a hydrate in the unlabelled form, since one expects that labeled and unlabeled to have the same physical properties. One is motivated to prepare this unlabeled hydrates because (1) drugs are normally administered in their unlabelled form (which is the form that mirtazapine is commercially available in) and (2) the hydrate is a standard pharmaceutical form as is shown by the secondary reference. Thus, the teaching that mirtazpines (albeit labeled) forms a hydrate would provide the motivation for preparing the unlabeled mirtazapine in a hydrate form for pharmaceutical use.

Response to arguments

Applicants arguments filed 09/01/2004 have been fully considered but they are not persuasive.

I. Applicants disagree with the Examiner's position that the method in which the mirtazapine product is isolated in Kaspersen et al., would naturally lead to a hydrate, even though Kaspersen et al. fail to teach or suggest that the final product is a hydrate. The examiner disagrees with applicants. Both applicants and Kaspersen use an extremely similar method, thus, it is presumed that the same hydrate product is formed from virtually the same crystallization method. Kaspersen *et al.* on page 1066 teaches the synthesis of mirtazapine and the crystallization of the mirtazapine (compound **1c**) from the crude product using charcoal, methanol/water solvent mixture to achieve colorless crystals. Applicants on page 6 (lines 5-6) also discloses mixed solvents such as methanol/water, plus charcoal to make crystals of a mirtazapine hydrates. The only difference between applicant's mirtazapine and Kaspersen's Org-3770 is that Kaspersen's compound **1c** is ^{13}carbon labeled, but the instantly claimed product requires that the mirtazapine be unlabeled. One skilled in the art would presume that labeled and unlabelled would crystallize in the same way.

In regard to applicant's argument that the processes of making hydrates (see Inventive Examples 1, 6, 8 and 11) are different from that of Kaspersen's, the examiner disagrees with applicants. This is a speculation. Whether a thin stream of water is added to the solution or the water is part of the water/methanol mixture in crystallizing the mirtazapine, it makes no difference in making hydrates. Applicants only have to

replicate Kaspersen (with or without the label; either is acceptable) and clearly on record show that the water from the crystallization process is not present.

II. Applicants argue by presenting the following yield calculation for the hydrates and the non-hydrate Kasperesn's mirtazapine compound disclosed "[^{13}C]-Org 3770 1c" on pages 1065-1066:

> First, Kaspersen et al. disclose at the last paragraph of page 1065 to the first paragraph of page 1066, i.e., column "[^{13}C]-Org 3770 1c", that 600 mg of Org 3770 was obtained as colorless crystals from 1.2g of 13a in the yield of 53%. This yield has been obtained by the calculation when Org 3770 is not regarded as a hydrate as explained below.
>
> Please note that the carbon atom is ^{13}C.
>
> - Molecular weight of 13a ($C_{17}H_{21}N_3O$): 300
> - Molecular weight of 1c which is not a hydrate ($C_{17}H_{19}N_3$): 282
> - Molecular weight of 1c which is a 1/2 hydrate ($C_{17}H_{19}N_3 \cdot \frac{1}{2} H_2O$): 291
>
> (i) Yield of 1c which is not a hydrate:
>
> (0.6/282÷1.2/300)x100 = 53(%)
>
> (ii) Yield of 1c which is a hydrate:
>
> (0.6/291÷1.2/300)x100 = 52(%)
>
> Therefore, it is clear that the mirtazapine compound 1c of Kaspersen et al. is not a hydrate, in contradiction to the Examiner's position.

The examiner disagrees with applicant's conclusion that "the mirtazapine compound 1c of Kaspersen et al. is not hydrate". Applicants are speculating, since this does not provide that Kaspersen's mirtazapine compound is non-hydrate. As shown, the yield results are rounded up to give whole numbers. This clearly shows that the results that are provided by applicants are not taken accurately, but the results are just a rough estimation.

The examiner disagrees with this calculation, since applicants only calculated for ½ hydrates but not for ¼ or 1/5 hydrates which are embraced. The result for n=5 becomes very close to 53.

For n = 5 or 1/5 hydrates the molecular weight is: 282 + 18/5 = 285.6 and the yield is: (0.6/285.6 x 300/1.2) x 100 = 52.57%. This could be rounded to 53% the same as the yield for the mirtazapine that is non-hydrated.

Applicants also argue: "Kaspersen et al. do not disclose or suggest the labeled compound is a hydrate." The examiner disagrees with applicants. Kaspersen does not have to suggest the labeled compound as a hydrate. There is no requirement for the obviousness rejection that Kaspersen has to suggest that the labeled compound as a hydrate. The compound is asserted to be inherently a hydrate because it is made via a method which applicants use to prepare hydrate. Even if Kaspersen did his yield calculation assuming that the material was non-hydrate that does not change the nature of the material. The evidence is already presented above and in previous Office Actions.

According to MPEP 2112.01:

> *Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).* [underscoring added]

Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

III. Applicants also argue: "Third, in the workup for compound 1c of Kaspersen et al., it is clear that Kaspersen et al. do not believe that the final product is a hydrate. Kaspersen et al. teach that: '[n]o impurities were detectable either on TLC, HPLC or GC', see page 1066, lines 7-8. Since the goal was to make mirtazapine, any water present would have been considered as an impurity. In addition, the peaks associated with the IR-spectrum described by Kaspersen et al. do not include a peak around 3000 cm^{-1} as is typically associated with the O-H stretching vibration in water". The examiner disagrees with applicants. First of all, the presence of water would not be spotted using TLC, HPLC or GC methods. Secondly, Kaspersen does not have to believe his final

product is a hydrate or not. It is also applicant's speculation that Kaspersen does not believe his final product is a hydrate. There is no mention whether Kaspersen's final product is non hydrate. It is up to applicants to show that Kaspersen's final product is a non hydrate. As far as we know the mirtazapine prepared by Kaspersen is inherently a hydrate, since it is made almost the same way as applicants.

The IR peaks reported by Kaspersen et al. does not necessarily show a complete spectrum of the labeled mirtazapine compound. Thus, it is incorrect to use the only 4 peaks reported by Kaspersen as the only peaks for the molecule. It is presumed that these peaks are the only important ones for the sake of the report, but not the "only" peaks for the molecule. In fact, in many IR data reports only important peaks are reported and usually peaks from water or other weak peaks are ignored. The peaks are not usually reported because they are very broad or they are not important because they are not part of molecule. Thus, applicant's argument that the IR-spectrum described by Kaspersen et al. do not include a peak around 300 cm^{-1} is not persuasive. Additionally, the examiner is providing six US Patents (5,284,857; 5,401,753; 5,397,790; 5,583,149; 4,524,146 and 5,468,768) as an evidence to rebut applicant's argument. In said US Patents, that disclose different type of hydrates the water peak around 3000 cm^{-1} was not reported when the IR data was taken using KBr that is the same as Kaspersen. Specifically, in US Patents 5,583,149 and 5,468,768 (column 17, lines 30-38 and column 17, lines 16-21) the IR(KBr) peaks for the hemifumarate hydrate compound were reported as 1660, 1575 and 1375 cm^{-1}. In US Patent 5,397,790 (column 14, EXAMPLE 23), the IR(KBr) peaks for the hemihydrate product were

reported as 1790, 1670 and 1600 cm^{-1}. Similarly, in US Patent 5,401,753 (column 12, EXAMPLE 18) for one-quarter hydrate of the title compound (n =1/4) the IR(KBr) peaks were reported as 1780, 1665 and 1610 cm^{-1}. A hydrate product of the pyrazolo[4,3-c]quinoline derivative in US Patent 4,524,146 (column 9, EXAMPLE 2), the IR(KBr) peaks were also reported as 800, 829, 870 and 880 cm^{-1}. A quarter hydrate product (n =1/4) in US Patent 5,284,857 (column 30, EXAMPLE 96) were also reported with an IR(KBr) peaks at 1667, 1658, 1638, 1613, 1600, 1568 and 1476 cm^{-1}. Note that the hydrates of said US Patents do not contain any IR(KBr) peaks at around 3000 cm^{-1}. It may be conventional to ignore peaks not part of the base molecule, or the water peak may have been broadened to the point where it was not seen, especially if the water amount was small.

Applicants also argue "[a]ssuming *arguendo* that the mirtazapine product of Kaspersen et al. includes water, the Examiner has not established reasonable grounds to conclude that the water would be present as a solvate or a hydrate. The Examiner will note that the inventive claims clearly set forth that the mirtazapine product is a hydrate." The examiner disagrees with this argument. Applicants and Kaspersen use almost the same method to prepare crystal of mirtazpines, thus, it is obvious that these two have the same characteristics (i.e. hydrates). The examiner has established reasonable grounds that Kaspersen's mirtazapine product as a hydrate (see above). Applicants assume that their mirtazapine that is prepared almost the same method as Kaspersen as a hydrate but not solvate, thus, the argument that examiner did not

establish whether the water present in solvate or hydrate form is not persuasive. It is up to applicants to replicate Kaspersen and show that Kaspersen product that includes water is not a solvate. Water present in a crystalline product is normally presumed to be a hydrate. Applicants have made the same presumption here.

Applicants indicate: "The present inventors for the first time found out the hydrates of an unlabeled compound. Moreover, they have for the first time found out anhydrous mirtazapine crystals having low hygroscopic properties and high purity by drying the hydrates of unlabeled compound...they have for the first time found out that the hydrates are important intermediates for preparing anhydrous mirtazapine crystals." The examiner disagrees with applicants, since the hydrate of the labeled compounds could just as well be important intermediates for preparing anyhydrous labeled mirtazapine crystals. Note that the argument: "[t]hey have for the first time found out anhydrous mirtazapine crystals having low hygroscopic properties" is not relevant, since the anhydrous form is not being claimed, and hence its properties are not relevant.

Applicants also argue that Kaspersen's mirtazapine compound is used for metabolic studies in animal and man for the determination of the bioavailability, the compound labeled ^{3}H, ^{14}C, and ^{13}C was needed.....labeled compounds prepared by Kapersen et al. are to be administered a single time for studies. There is no teaching or suggestion that labeled compounds are continuously administered to a patient as a therapeutic substance." The examiner disagrees with applicants. As applicant's argument indicates, it seems that all labeled compounds are unfit for pharmaceutical

purposes to treat certain diseases. As far as we know, the labeled and unlabeled crystal mirtazapine compounds can be administered to the body for treatment purposes. The use of labeled compound in research is in fact based on the assumption that they act the same as non-labeled. If they did not so act, the research would be pointless.

Applicants further argue: "Kaspersen et al. teach the preparation of these labeled compounds for use in metabolism studies. However, to remove the labels of Kaspersen necessarily renders the compounds unsuitable for their intended purpose. As such, there would be no motivation to modify the labeled compounds of Kaspersen et al. to use them in treatment." The examiner disagrees with applicants because the intended purpose for both the labeled and unlabeled mirtazapines are not significantly different one from the other. Note that the labeled compound was prepared in order to study what the known unlabelled compound does in the body. It would have been obvious to one skilled in the art use the unlabeled compounds, since the Kaspersen's labeled mirtazapine are used for metabolic studies. The examiner does not assert that the unlabeled compounds could be used for Kaspersen' purposes.

Applicants also argue: "The prior art must contain a suggestion to make modifications, and there is clearly no suggestion by Kaspersen et al. to make the modifications. The mere fact that a prior art device or process could have been modified, does not make the modification obvious unless the prior art suggested the desirability of the modification. See e.g., In re Gordon, 221 USPQ 1125, 1127 (Fed. Cir. 1984) and Ex parte Tanksley, 37 USPQ2d 1382 (BPAI 1994)." The examiner disagrees with applicants, since this is not relevant to this issue. This is not a device case.

Kaspersen does not have to suggest any modifications. The fact that antidepressants administered clinically are always non-labeled could provide all the motivation.

Applicants also argue "[s]ince the labeled compounds are not used for therapeutic pharmaceuticals, there is no motivation in Kaspersen et al. to produce and ascertain the physical properties of the labeled compound in order to use unlabeled compounds for therapeutic pharmaceuticals." The examiner disagrees with applicants. Applicants are speculating. There is no evidence that Kaspersen used the labeled mirtazapine hydrates because the labeled could not be used for therapeutic purposes. Kaspersen's labeled mirtazapine are used for metabolic studies that will give way for the use of the unlabeled compounds in the treatment.

In addition, the examiner would like to refer to the following review article: {Thermochemica Acta 248 (1995) 61-79} that shows that hydrates form an integral part of many solid dosage forms. Also on page 77, the authors conclude: Hydrates form an integral part of many pharmaceutical dosage forms" that indicate that the hydrates are the preferable way to make pharmaceutical compositions. The authors also conclude: "It is evident that hydration or dehydration of a pharmaceutical solid during formulation development or in a final dosage form may adversely affect the physical, chemical and /or biological performance of a pharmaceutical product." Thus, if dehydration adversely affects the physical and/or biological performance of a pharmaceutical product, a pharmaceutical dosage in a hydrated form would be preferable. Therefore, the argument that Kaspersn et al. does not disclose or suggest that crystals of compound

1C as hydrates is not persuasive, since it is obvious to one skilled that the hydrates are the preferable form or conventional way of making pharmaceutical compositions. The anhydrates of mirtazapine crystals are obvious over the hydrates mirtazapine crystals.

Since the hydrate of the labeled compounds could just as well be important intermediates for preparing anhydrous labeled mirtazapine crystals and the fact that the hydrates are the conventional way of making pharmaceutical formulation as shown above, the obviousness rejection is proper. Note that obviousness can be for any purpose. Here, since unlabeled mirtazapine is known pharmaceutical, its unlabeled hydrate can be obvious for pharmaceutical purposes, even if it is not obvious for metabolic studies.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

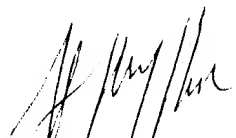
Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (571) 272-0674. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.



Kahsay Habte, Ph. D.
Examiner
Art Unit 1624

Mark L. Berch
Primary Examiner
Art Unit 1624

KH
September 15, 2004